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Nocardia brain abscess in a 49-year-old woman with pulmonary alveolar proteinosis: a case report

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Abstract

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disease, associated with functional impairment or reduced decrease in the number of alveolar macrophages. Primary or autoimmune type is the most common. The impaired function of immune system made these patients susceptible to opportunistic infections like nocardiosis. A 49-year-old Iranian previous healthy woman was admitted with seizures and a history of one-month respiratory symptoms prior to the seizure attack which was treated as pneumonia. Chest CT and brain MRI were performed, which revealed 'honey-comb' pattern and a brain abscess respectively. Specimen from brain showed Nocardia infection. Therefore, the pulmonary involvement was interpreted as nocardiosis and treated with trimethoprim/sulfamethoxazole (TMP/SMX). After one year, there was no improvement in pulmonary condition in terms of radiologically and clinically. A CT-guided biopsy from lung lesions was performed and the pathology exam confirmed the diagnosis of PAP. The patient was treated with whole lung lavage and after one-year follow-up she remains symptom-free. PAP is a rare condition, which can be easily missed. Our case highlights the importance of thinking of rare conditions like PAP in patients present with opportunistic infections especially those who are immunocompromised or had occupational exposures to substances like silica. Considering this diagnosis, particularly, when we have no response to empiric anti-biotic therapies, it can lead us to faster diagnosis and more appropriate cure.

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Introduction

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disorder characterized by the presence of massive amount of proteinaceous, periodic acid/Schiff (PAS)-positive material in the alveolar spaces due to the abnormal function of alveolar macrophages in surfactant clearance, leading to progressive impairment in gas exchange. It usually presents with Breathlessness (dyspnea) and cough (1, 2). Primary or idiopathic PAP supposedly caused by an autoimmune mechanism with antibodies against granulocyte-macrophage colony stimulating factor (GM-CSF) is the most common type (3, 4). The abnormal function of immune system as a key mechanism in primary PAP, makes patients susceptible to opportunistic infections such as *Nocardia*, mycobacteria and fungal pathogens(5). *Nocardia* is an uncommon Gram-positive bacterium causing variable complications from pulmonary involvement to disseminated forms with brain abscess (6, 7). As immunocompromised patients are increasing in societies, the association between presentations of opportunistic infections e.g. nocardial brain abscesses and rare medical diseases such as PAP should be considered.

Key point

In the presence of diffuse bilateral alveolar opacities on chest imaging concomitant with disseminated infections by opportunistic infection like the nocardial brain abscess described in our patient, pulmonary alveolar proteinosis is better to be considered and excluded.

Case Presentation

A 49-year-old woman was admitted to the hospital in March 2019 with complaints of nausea, headache and two episodes of generalized tonic-clonic seizures accompanied by chronic cough and dyspnea. She was a non-smoker housewife with no past medical history. She had a history of dry cough and dyspnea one month prior to her recent admission, which was treated as pneumonia with a 2-week course of antibiotics.

On physical examination, our patient was found to be febrile (38°C), tachycardic and tachypneic. Lung auscultation revealed a few scattered crackles. Neurological and other physical examinations were normal. Initially

laboratory test results showed a white blood count of $7\times10^3/\mu L$, hemoglobin of 15 g/dL, ESR of 14 mm/h and C-reactive protein (CRP) of 2+, other laboratory tests were normal.

A chest CT scan was obtained that showed bilateral diffuse ground-glass opacifications with thickened intralobular structures creating the so-called 'crazy-paving' pattern (Figure 1). Discovering the reason of neurological presentations, MRI was performed which revealed a ring lesion with surrounding vasogenic edema in favor of brain abscess. Lung and brain involvement at the same time raised the possibility of opportunistic infections such as *Nocardia*, mycobacteria and fungal pathogens like *Cryptococcus*.

For both treatment and diagnostic purposes, brain abscess evacuation and lung lesions biopsy were suggested but she refused. Therefore, she received parenteral antibiotics (meropenem and vancomycin) in addition to trimethoprim/sulfamethoxazole (TMP/SMX) and was eventually discharged with anti-epileptic drugs.

On the 10 day after the last admission, the patient came with another attack of seizure associated with left facial palsy and persistent cough and dyspnea. This time she went under brain abscess drainage. The brain biopsy was cultivated and examined by smear microscopy which indicated rod-shaped, branching, filamentous, gram-positive organisms suggestive of *Nocardia*. A chest CT was obtained but there was not any improvement in lung infiltrations, therefor a fiberoptic bronchoscopy was performed and samples from bronchoalveolar lavage (BAL) were examined for *Nocardia*, *Cryptococcus*, *Mycobacterium tuberculosis* and also a cytology for malignancy but all of them turned up negative. The patient went under CT-guided biopsy from peripheral lung lesions but the result was non-diagnostic; therefore the patient was treated as pneumonia with a 20-day course of meropenem, vancomycin and also TMP/SMX for brain nocardial infection and was discharged with one-year course of TMP/SMX in order to prevent abscess development and covering possible nocardial lung infection and anti-epileptic drugs ceased (Figure 2).

After one year, she attended for follow up in May 2020. She had no neurological symptoms during this time but her dry cough and dyspnea had no change. A chest CT was performed; surprisingly the lung lesions did not show any remission despite one-year consumption of TMP/SMX. As we are now in the pandemic of coronavirus, COVID-19 infection was considered due to the ground-glass pattern, but according to the clinical manifestations, disease chronicity and unchanged pattern of lung CT involvement in comparison with last CT, COVID-19 excluded. Consequently, the patient referred to a pulmonologist and a CT-guided biopsy from peripheral lung lesions was performed and a specimen sent for pathology. The pathology examination showed alveoli filled with PAS-positive proteinaceous material suggestive of PAP. Finally, with the diagnosis of PAP, it was decided to treat her with whole lung lavage (WLL). After the WLL, resolving of lung lesions was conspicuous and after one year of follow-up, the patient remains free of symptoms.

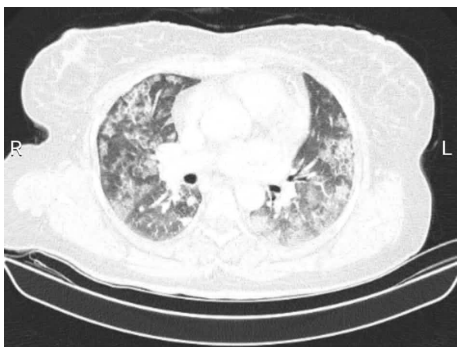

Figure 1. Chest HRCT of the index case showing bilateral diffuse ground-glass opacifications creating the 'crazy-paving' pattern.

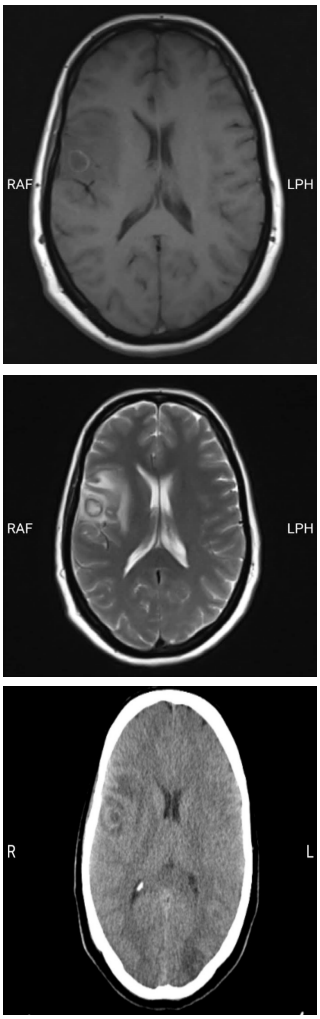

Figure 2. T1- weighted MRI image of brain of the index case demonstrating the right temporal ring-enhancing lesion with surrounding vasogenic edema suggestive of brain abscess.

Discussion

The prevalence of PAP is estimated to be 3.7 cases per million based on data gathered from case reports and small series. It can occur in all age groups but the median age at the time of diagnosis is 39. Men are affected more frequently than women with male: female ratio 3:1. Smoking is an important predisposing factor too (8, 9).

There are three clinical forms of PAP: congenital (2%), primary (also regarded as idiopathic or acquired 90%) and secondary (up to 10%) (8). Congenital PAP supposedly is caused by genes mutation encoding surfactant proteins or by the absence of granulocyte macrophage colony-stimulating factor (GM-CSF) receptor (2,4). In primary PAP antibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF), receptor deficiency or gene mutation making macrophages incapable of surfactant clearance (2,4,10). Secondary PAP is caused by different clinical conditions or underlying diseases leading to a reduction in the number or function of alveoli macrophages. These conditions include immunodeficiency disorders like HIV, hematologic malignancies and occupational exposures to flour, wood or silica dust (8, 10).

The clinical presentation of PAP has a wide range from asymptomatic to non-productive coughs and progressive exertional dyspnea that may be associated with malaise, weight loss and low-grade fever or in severe cases leads to respiratory failure (1,8). PAP patients are more prone to recurrent lung infections. An inflammatory condition and prominent fever needs an exact approach due to a possibility for an underlying infection presumably caused by an opportunistic microorganism like *Nocardia*, mycobacteria or *Cryptococcus*.

Physical examination is usually non-specific but a few patients may exhibit fine crackles in lung auscultation. Clubbing and cyanosis are rare but have been reported (1,11).

The radiographic findings have no specific features to suggest the diagnosis of PAP, however bilateral central and symmetric lung opacities or perihilar patchy consolidations exhibit a 'bat-wing' configure could raise the possibility of PAP. Multifocal asymmetric opacities are less common but could exist. Although diffuse consolidations suggest interstitial pulmonary edema, plural effusion and lymphadenopathy are absent (10, 12).

Chest CT scan reveals interlobular septal thickening superimposed on areas of ground-glass opacifications and producing the so-called 'crazy-paving' pattern. This pattern was first believed to be pathognomonic for PAP, later it has been found in other conditions such as bronchoalveolar carcinoma (13), lipoid pneumonia (14), lymphangitic carcinomatosis, P jirovecii pneumonia, alveolar hemorrhage and radiation- or drug-induced pneumonitis. Given this wide differential diagnosis, an exact diagnostic evaluation is needed (14, 15).

Laboratory studies in PAP usually are normal, but a few findings along other clues can guide us to the diagnosis. Elevated levels of LDH, KL-6 mucin, SP-A, SP-B and SP-D appear to correlate with disease activity, however, their diagnostic value for PAP is limited as they are found in other pulmonary diseases; therefore, they should be interpreted along with other evidence (4,8). However, antibodies against GM-CSF were present in all serum and BAL fluid samples from idiopathic PAP patients, however were not exist in those with secondary and congenital PAP, hence anti-GM-CSF antibodies could provide a powerful diagnostic tool for the disease (16-18). Pulmonary function test (PFT) shows a restrictive pattern and could provide a clue reaching to diagnosis(19).

The diagnosis can be established on the basis of the 'crazy-paving' appearance on the high-resolution CT (HRCT) of the chest, in conjunction with fluid examination obtained from bronchoalveolar lavage (BAL) and/or by lung biopsy. Open lung biopsy is less commonly required now, as, a diagnosis of PAP can be made in majority (75%) of suspected cases by the findings of a 'milky' effluent from BAL. This fluid containing abundant amount of granular acellular eosinophilic proteinaceous material, with abnormal 'foamy' macrophages engorged with PAS-positive intracellular inclusions (20-22). Generally, fluids from BAL are microbe-free and this shows infections in these patients are a secondary event rather than the initiating process (8).

Treatment of PAP generally depends on the underlying pathology, as for congenital form conservative treatment and occasional lung transplantation is used. For secondary PAP abstention from environmental agents such as silica and also treating the underlying diseases caused immunodeficiency is the best approach(10). Treatment for primary PAP has evolved from the use of multiple non-specific agents, to the physical removal of the proteinaceous material out of lungs under general anesthesia called WLL and also a more specific therapy with recombinant GM-CSF. WLL which was reported by Ramirez et al, is now considered the treatment of choice (23). It improves macrophage's function and reduces the incidence of opportunistic infections. Significant improvements in clinical, physiologic and radiologic patterns have been reported after the first therapeutic lavage in 84% of PAP patients. GM-SCF replacement is still controversial due to the possibility of bone-marrow suppression in long-term use and needs further investigations (8-10, 24).

PAP patients have been known to be at great risk of secondary infections with a variety of organisms. 'Unusual' organisms like Nocardia are more frequent in these patients than Common bacteria causing community and hospital infections like streptococcus. Disseminated and particularly, nervous system involvement generally caused by either Aspergillus or Nocardia, indicates the fact that the predisposition to infection among primary PAP patients is systemic in nature rather than local changes in

the lung. This importance suggests the systemic role of neutralizing antibodies against GM-CSF (8).

In addition, COVID-19 pandemic should be mentioned whereas, chest-CT findings could be misleading and causing a serious pulmonary disease misdiagnosed as COVID-19. A broad range of CT patterns exist. Besides ground-glass opacities and consolidations, 'crazy-paving' pattern is a frequent manifestation. Hence it should be interpreted with patient's clinical presentation (25-27).

Conclusion

Since the rarity of PAP, many cases were missed until they worked-up due to an infection. Therefore, in the presence of diffuse bilateral alveolar opacities on chest imaging concomitant with disseminated infections by opportunistic infection like the nocardial brain abscess described in our patient, PAP is better to be considered and excluded (5).

Authors' contribution

MB and SM were the principal investigators of the study and were included in preparing the concept and design, revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient gave the consent to publish as a case report.

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